Case Reports

Pemphigus Vulgaris and Plasma Exchange

Role of Intercellular Antibodies

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CLINICAL AND experimental evidence implicates intercellular IgG antibodies in the pathogenesis of pemphigus vulgaris.[1-3] Acantholysis in fresh skin explants has been produced experimentally by incubation of whole serum with the purified IgG fraction of serum from patients with pemphigus vulgaris.[4,5]

Clinical improvement has been reported to correlate with loss of acantholytic activity and decreased antiepithelial antibodies in pemphigus patients particularly when measured by direct immunofluorescence;[6] this has led to trials of treatment with plasma exchange.

A patient with active pemphigus vulgaris refractory to steroid therapy was treated by plasma exchange in an attempt to reduce pemphigus antibodies and bring about clinical remission. Plasmapheresis was effective in reducing antibody titers measured by both direct and indirect methods. This did not correlate with suppression of active disease.

Report of a Case

A 56-year-old Spanish-American woman presented with 30% of her body surface area covered with progressive bullae. These had been present for nine months and her scalp, face, trunk, extremities and oral and vaginal mucosa were involved. Her pemphigus vulgaris (shown by biopsy) started two years earlier and had been treated successfully with steroid injections and antibiotics at that time.

Initial histologic examination showed intraepidermal bullae with acantholysis of epidermal cells; direct immunofluorescence showed intercellular IgG deposits in the epidermis. Circulating epithelial antibody levels were 1:160 and 1:320 before the initiation of therapy. An antinuclear antibody test was negative.

Administration of 100 mg a day of prednisone was begun and increased to 120 mg after the first week, 200 mg after the second and 300 mg after the third without improvement. Plasma exchange (performed by B. Ferdinando, RN, D. Phillips, RN, and E. Wilson, RN, of United Blood Services, Albuquerque) was then started twice a week. Interruption of plasmapheresis and decrease of the prednisone dosage to 100 mg a day were required because of *Neisseria meningitidis* pneumonia. New bullae developed, but the pneumonia responded to treatment with aqueous penicillin G. Plasmapheresis and prednisone therapy were resumed, but new bullae continued to develop despite increases in prednisone dosage to 800 mg a day over a period of four weeks. Intramuscular aurothioglucose therapy of 50 mg a week, started at eight weeks, and cyclophosphamide at 50 mg per day, started after 12 weeks, did not prevent new bullae, and the patient died. Permismission for autopsy was denied. Death appeared to be related to both pneumonia associated with immunosuppression and active pemphigus.

Methods

Plasma exchange was accomplished using a continuous-flow process on the IBM 2997 cell separator. Two liters of plasma (approximately one plasma volume) were removed and replaced by 5% albumin, fresh-frozen single donor plasma and saline.

Before and after each plasma exchange, a serum specimen was assayed for intercellular antibodies by indirect immunofluorescence using a technique described by Beutner and co-workers.[7] Monkey esophagus was used as substrate. A positive control pemphigus serum as well as negative control serum were used to test the substrate. The serum was tested, beginning at 1:10 and 1:100 dilutions. Studies were carried out in the laboratory of K. S. K. Tung, MD (Albuquerque).

Tissue specimens for direct immunofluorescence were obtained from perilesional skin and processed by the technique of Beutner and associates.[7] Commercially available goat antihuman IgG, IgM, IgA and C3 and fibrinogen with a fluorescein-to-protein ratio of 3.0 ± 0.5 to 1 were used. Tissue specimens for direct immunofluorescence were taken of perilesional skin with a 4-mm punch biopsy and transported in a citrate buffer solution containing ammonium sulfate, *N*-ethyl maleimide and magnesium sulfate.[8] Direct immunofluorescence testing was always carried out within one week in the laboratories of K. S. K. Tung, MD, and D. L. Tuffanelli, MD (San Francisco).

Serum samples were sent to Dr John R. Schiltz, Case Western Reserve University, Cleveland. IgG was prepared from the pooled samples and tested for ability to cause acantholysis in cultured normal human skin.[4]

Results

The titers of circulating intercellular antibodies before and after the plasmapheresis are illustrated in

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Figure 1. The titer of intercellular antibodies, as high as 1:320, dropped by two dilutions, a reduction of approximately 50% in circulating levels of antibodies, with each treatment. A rebound was seen following the first two procedures but not thereafter. Following the seventh procedure, levels consistently remained negative.

Tissue initially showed direct immunofluorescence. Ten weeks later, when the patient had active pemphigus vulgaris but indirect immunofluorescence testing was negative, specimens were negative for direct immunofluorescence.

IgG prepared from the original pool caused suprabasilar acantholysis after 72 hours in culture.

Discussion

Exchange plasmapheresis has been used successfully in patients with pemphigus vulgaris.[9-13] Four of the five patients reported responded on various schedules of plasma exchanges with various accompanying immunosuppressive drugs. The one patient in whom the therapy failed had disappearance of antibodies, but treatment was terminated due to problems with vascular access.[13]

The role of the IgG antibody in the pathogenesis of pemphigus has been shown by its ability to produce histologic lesions in vitro,[5] cause loss of adhesion in cultured mouse epidermal cells,[14] detach mouse epidermal cells grown in serum[15] and induce disease in mice by passive transfer from patients.[3] Moreover, a proteolytic enzyme recovered from cultures with the antibody has been termed "pemphigus acantholysis factor."[16] The hydrolysis of the cell surface by pemphigus acantholysis factor may result in loss of adhesion and ultimate acantholysis. Naturally occurring inhibitors to this action have also been described.[15]

Our patient's failure to have reduction of disease activity with decrease in serum levels and disappearance of tissue levels of intercellular antibody suggests that removal of antibodies may not be adequate therapy. This report confirms a previous observation[6] that the circulating antibody level measured by indirect immunofluorescence as a marker of disease has limitations in the setting of plasma exchange. Unlike in other reports, the change from positive to negative in direct immunofluorescence of perilesional skin did not correlate with clinical success.

Moreover, plasma exchange therapy was not clinically successful. Possible explanations for our lack of success include the following: (1) Circulating plasma inhibitors may have been removed along with the antibody. (2) The antibody may be a marker of the disease rather than truly pathogenic. (3) The patient's disease, which was unresponsive to all therapy, may have been too advanced to draw a conclusion from this trial of plasma exchange.

The antibody was shown to be active in the tissue culture system; therefore, it is surprising that its disappearance was not associated with clinical improvement. High doses of prednisone (given after plasma exchange treatment to prevent removal) combined with plasma

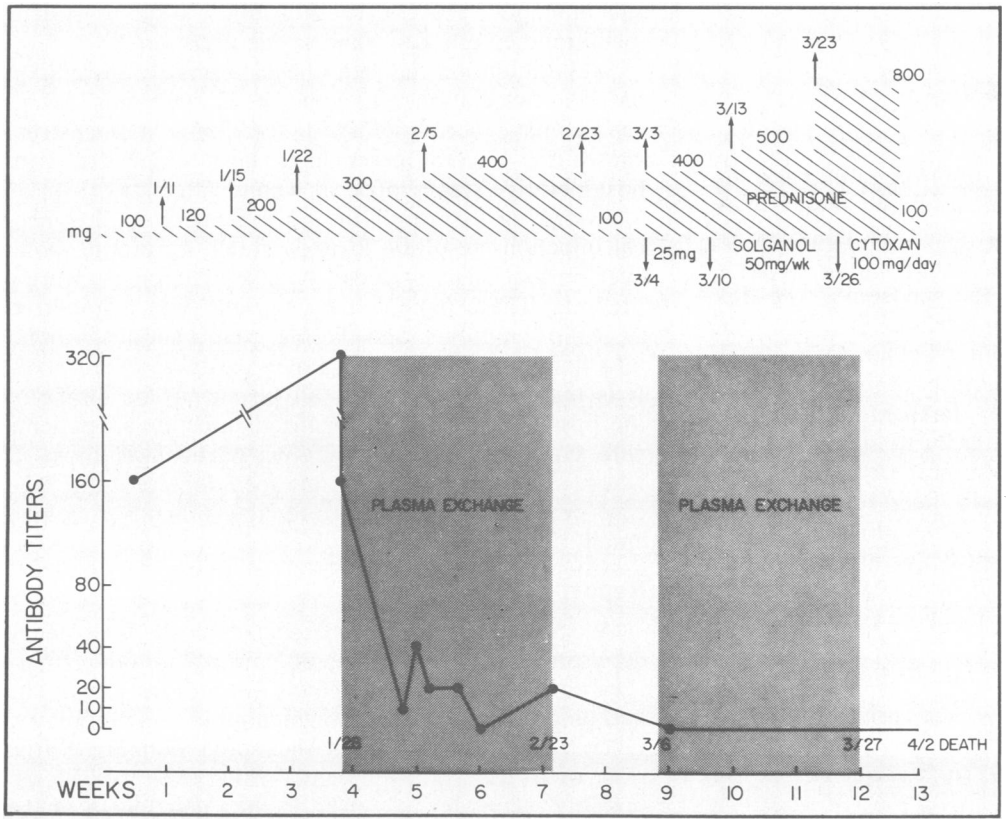

Figure 1.—The patient's clinical course, circulating antibody titers and treatment are shown.

exchange were not clinically effective; gold and cyclophosphamide added sequentially because of treatment failure were also ineffective. Ultimately the patient died with new bullae appearing in previously normal skin and previously healed areas along with crops of blisters. The role of the pemphigus antibody in vivo even when active in tissue cultures in vitro is therefore less certain than is implied in recent studies.[3] Factors other than the antibody, such as certain enzymes,[14] may be important in pathogenesis of this disease.

The role of plasma exchange, used in this case exhaustively over two months, is uncertain. Whereas it has been rapidly successful in other cases,[9-13] it did not prove of clinical benefit in this case. However, this patient failed to respond to any known treatment modality; thus, plasma exchange is not disproved as a possibly successful therapeutic maneuver. The combination of successful antibody removal with lack of clinical success suggests that the mechanism of any benefit found may be more complex than antibody removal. Indeed, the data in this case suggest that when plasma exchange therapy is used, certain markers of disease may lose their clinical value. The procedure can conceivably remove such markers without providing clinical benefit. Thus, clinical benefit that occurs after plasma exchange in many diseases should not be assumed to be due to removal of pathogenic substances.

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Toxic Shock Syndrome Due to Occult Postoperative Wound Infection

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DURING THE past several years, both the public and the medical community have come to know toxic shock syndrome as a potentially lethal symptom complex associated with tampon use in menstruating women. From the first report defining the syndrome,[1] the link with tampon use has been emphasized.[2-13]

There has been debate about whether toxic shock syndrome represents a new disease or merely a significant increase in a formerly unrecognized disease entity.[14] It does bear some similarity to staphylococcal scarlet fever in that both syndromes are associated with staphylococcal bacteria and skin rash formation.[14-20] However, staphylococcal scarlet fever does not cause the remainder of the clinical spectrum of toxic shock syndrome, and it does not show particular association with tampon usage. In fact staphylococcal scarlet fever has been reported in association with a wide range of staphylococcal infections, including empyema, fasciitis, subcutaneous abscess, peritonsillar abscess, mucus membrane colonization and septic abortion.[20]

While attention has been given primarily to tampon usage in association with toxic shock syndrome, recent reports have been published describing nonmenstrual causes.[20-32] Several cases have been associated with postoperative staphylococcal wound infections.[22,24-28]

A striking feature of the postoperative staphylococcal infections resulting in toxic shock syndrome, however, is that signs of local wound infection are rarely present.[8] These patients may present with generalized systemic symptoms, and the fact that a surgical wound infection might be the cause may easily be overlooked. It is therefore crucial that all physicians be aware of the possibility of occult localized infection in patients with symptoms of the syndrome, particularly those in whom a surgical procedure has been done recently. The case presented below illustrates the difficulty this may entail.

Report of a Case

A 35-year-old woman presented to the emergency department with complaint of nausea, vomiting, diarrhea and a rash. Approximately six months earlier she had undergone bilateral augmentation mammoplasty. Over the next few months she noted thinning of the skin over the right implant, which was considered possibly secondary to steroid in the outer lumen of the

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